Title & Detailed Synopsis of the Proposed Ph.D. Thesis

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GREEN-INSPIRED DESIGN AND SYNTHESES OF ORGANIC COMPOUNDS WITH BIOLOGICALLY RELEVANT MOLECULAR ARCHITECTURE

a) Origin of the research problem

Natural product-inspired organic molecules containing privileged structural motifs are of prime importance in the modern drug discovery and development processes, and as result of which numerous synthetic molecules have currently been established as useful dugs against deadly diseases. Still we need so many new molecules of potent bioactivities required to manage drug-resistant diseases and also new drug molecules and leads to mange diseases for which the remedies are not available or limited. Hence, a dedicated research in the field of synthetic organic chemistry is going-on with a motto to have organic molecules with new kinds of molecular architectures having a promise to exhibiting effective pharmaceutical properties. Among various such organic scaffolds, heterocyclic compounds are one of the most well-known for their inherent biological activity and applications in diverse fields, reflected by the fact that this class of compounds constitutes more than half of known organic molecules. So, new molecular architectures bearing either heterocyclic or non-heterocyclic or both of them may show some desired biological potency, and endeavors should be exercised in developing such types of new molecules, indeed!

At this present juncture of chemical synthesis, chemists restrict them not only in creating new molecules but at the same time they are much passionate about how these molecules can be generated! Yes, we are speaking about the 'green concepts' behind the organic synthesis! Today, public is equally aware of the hazardous substances used and generated by the chemical processes. Our natural environment needs to be protected from ever increasing chemical pollutions associated with contemporary lifestyles and emerging technologies. The fundamental challenge for developing a sustainable chemical enterprise will be finding creative ways to minimize human exposure to, and the environmental impact of, harmful chemicals while enhancing scientific progress. A new approach emphasizing pollution prevention through the design and use of cleaner products and processes can help the chemical enterprise to achieve a sustainable future.

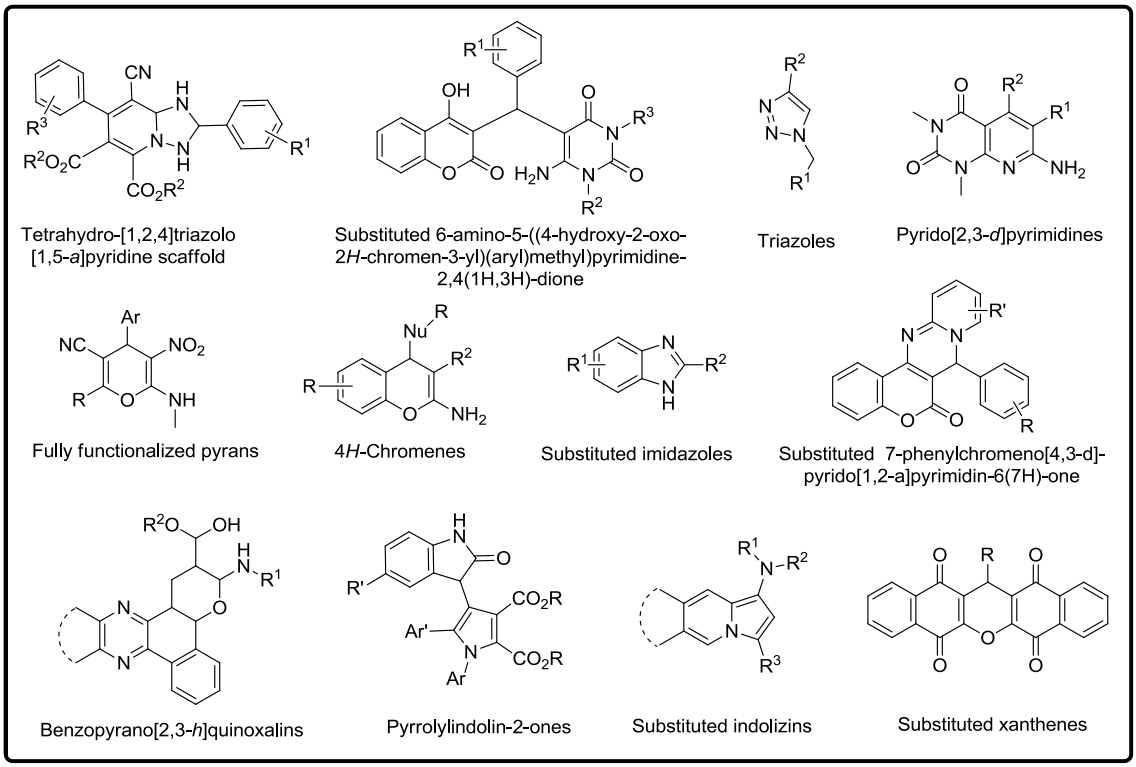
Dedicated research endeavors have yielded innumerable green products and processes so far, and such well-documented quarter century advances in the fields of *green chemistry and green engineering* have framed a solid platform that motivates and empowers the younger researchers to carry forward the *flag* with much enthusiasm and potential! Aiming on the development of processes for sustainable production of chemicals and materials, innovations in green chemistry and engineering, at molecular, process, and systems levels, are reported at an ever-increasing rate. Hence, the next 25 years of *green and sustainable chemistry* is expected to become more powerful, promising and potent finding much applications in industrial sectors. During the recent past, various greener pathways as alternatives to traditional chemical syntheses and transformations have been invented in diverse fields of chemistry to attain sustainability through newer concepts such as step- and atom-economy and E-factor. Greener features in designing an alternative protocol for useful organic molecules and/or materials include the use of bio-renewable resources, benign reaction media (use of greener solvents or no solvent), recyclable magnetic heterogeneous catalysts or no catalyst, minimization in by-products or waste generation with efficient isolation of target product, and consideration of energy-efficiency in performing a chemical reaction by judicious screening of reaction conditions capable to carry out the transformation at ambient conditions or to make use of microwaves (MWs), ultrasound (US), visible lights and mechanical mixings (ball-milling) as *green tools* for alternative heating and activation of reactants.

Under this very strong background, the present investigator is deeply motivated to undertake research drives to develop green-inspired synthetic routes for a handful of new series of organic molecules having biologically relevant molecular architectures during the tenure of his Ph.D. programme.

b) Objectives of the present work plan

- To develop eco-friendly MCR methodologies to achieve high atom-economy, avoiding multi-step complex processes either at room temperature and atmospheric pressure or under the direct application of any of the alternative energy sources
- To perform synthesis of organic scaffolds under focused ultrasound irradiation
- To perform synthesis of organic scaffolds using ball-milling technique
- To perform synthesis of organic scaffolds using visible light as energy source
- To use nontoxic/less toxic and easily available chemicals as starting materials
- To use environmentally benign, cost-effective and easily available catalysts that could be recycled and reused
- To develop non-toxic or less toxic catalyst-systems
- To use water and/or aqua-organo mixture (e.g. water-ethanol) as solvent
- Easy purification of the final products avoiding chromatographic separation

Some targeted organic scaffolds of interests:



Scheme 1: Some targeted heterocyclic scaffolds of our interest

Point-wise summary of the major parts of the present work plan:

- Selection of targeted heterocyclic motif (**Scheme 1**) and designing its functionalized libraries
- Retroanalysis of the target motif and selection of cheap and commercially available substrates
- Designing for energy-efficient reaction protocols: optimization of catalyst and solvent media under suitable energy-efficient technique preferentially
  - at room temperature
  - under ball-milling
  - under ultrasound irradiation
  - visible light driven reaction
- Application of the newly developed protocol in synthesizing more complex libraries of interest

Planning to consider few more green chemistry parameters like:

- introduction of novel one-pot multicomponent technique
- to verify the reaction under catalyst-free condition
- use of efficient, non-toxic, commercially available, cheap catalyst
- use of solvent-free condition or to use suitable green solvents like water/ethanol/glycerol/PEG

c) General methodology to be followed

Simple experimental set-up is to be developed for one-pot syntheses of targeted heterocycles (**Scheme 1**). The substrates and the catalyst (or catalyst free condition) will be added in a reaction vial (at a time or in a sequential manner). If needed suitable solvent will be added into the reaction mixture. The reaction mixture will be stirred magnetically at room temperature. The progress of the reaction will be monitored by TLC/PMR. After completion, the reaction mixture will be settled down and the solvent will be removed under reduced pressure, and the residue will be purified simply by recrystallization and/or by column chromatographic technique. For characterization of the synthesized heterocycles, their detailed spectral studies including FT-IR, ^{1}H-NMR, ^{13}C-NMR, DEPT, HR-MS as well as elemental analyses will be performed. In certain cases, X-ray analysis of unit crystals as to be developed of the products will also be taken care of! Similar method will be used in case of ultrasonic irradiation.

Under grinding condition the reagents, substrates and catalyst (normally solid basic support) will be mixed in a ball-miller under solvent free condition. By definite programming, the reaction mixture will be subjected to grinding with pre-given speed and time. Before introduction of the reaction mixture, the particular ball-size will be chosen. After the completion, the reaction routine work up procedure will be followed to get the final products.

d) Future prospect

The research outcomes would embody a considerable amount of new works relating to the development of green methodologies for a number of novel biologically relevant heterocyclic compounds which would attract researchers from various multi-disciplinary fields for their further studies, particularly on the physio-chemical properties, in silico biological potentials, experimental (in vitro and in vivo) studies on their potential pharmaceutical efficacies and also use of the protocols as developed for library synthesis of lead drug candidates.

e) References

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